Neonatal septicemia in tertiary hospitals in Konya, Turkey

Sepsis and newborn

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Abstract

Aim: Neonatal sepsis is one of the leading causes of mortality and morbidity in the developing world. The present study aims to determine the incidence and risk factors of neonatal sepsis in a single center over a four-year period. Material and Method: This is a retrospective study of all cases of culture-proven neonatal sepsis admitted in the neonatal intensive care unit of a single center between January 2013 and December 2016. Clinical features, risk factors, microbiological and biochemical results, and mortality rates were recorded. Associations between risk factors and mortality were investigated. Results: The prevalence rate of neonatal sepsis was 2.7 per 1000 live births (94/30545) and 9.3 per 1000 neonatal admissions (94/10133). Low birth weight (≤ 2500g) was recorded in 79 (84%) neonates with sepsis. There was at least one risk factor in all cases. Gram-negative bacteria were more frequently isolated than gram-positive bacteria (63.8% (60/94) vs. 29.7% (28/94)). Klebsiella pneumonia was predominant in both early-onset sepsis and late-onset sepsis (53% (16/30), 29.7% (19/64) respectively). Late-onset sepsis episodes attributed to Klebsiella pneumonia were associated with the highest sepsis-related mortality (41.7%). Discussion: Klebsiella pneumonia was found to be the most common agent in neonatal sepsis and responsible for sepsis-related mortality in this study. Prevalence of neonatal sepsis, its pathogens and risk factors differ in different parts of the world. Region-specific strategies to prevent new infections should be encouraged.

Keywords

Neonatal Sepsis; Neonatal Intensive Care Unit

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Introduction

Neonatal sepsis is a clinical syndrome that occurs during the first months of life and is associated with a high rate of mortality when the diagnosis is delayed [1]. In spite of recent advances in health care units, neonatal sepsis is still an important cause of death and morbidity in the neonatal intensive care unit (NICU). Signs and symptoms of neonatal sepsis are often nonspecific thus making its clinical diagnosis challenging. Isolation of a bacterial pathogen from the bloodstream is the gold standard for diagnosis. However, due to the difficulty with growing pathogenic microorganisms in the blood, assistive diagnostic methods based on clinical and laboratory findings have been proposed in addition to blood cultures [2].

The frequency of neonatal sepsis, risk factors, and resistance against antimicrobial agents may be different in each unit [2]. Causative microorganisms differ from one group to the other and can vary over time even in the same clinical setting [3]. Recently, the most frequently reported causative organisms for neonatal sepsis are gram-positive bacteria followed by gram-negative bacteria such as *Klebsiella pneumonia* and *Escherichia coli*. Fungal etiologies are less commonly reported [4].

The aim of the present study was to evaluate the incidence of neonatal sepsis, characterize the etiological agents of neonatal sepsis, and determine risk factors for sepsis in the NICU of a single center.

Material and Method

The medical records of all neonates who were admitted to the NICU of a single center between January 1, 2013 and December 31, 2016 were reviewed. During the study period, all exposed neonates with clinical signs and symptoms of sepsis at the time of admission or who developed sepsis during their hospital stay were assessed and included in the study.

Cases of sepsis were classified according to the infant's age, the growth of potentially pathogenic organisms from blood at the time onset of clinical and laboratory findings consistent with infection symptoms: early-onset sepsis (EOS) (≤ 72 hours of life) and late-onset sepsis (LOS) (> 72 hours of life) [5]. Blood cultures were taken routinely when the baby was admitted to the NICU with the suspicion of having an infection.

Demographic characteristics, clinical and microbiological variables at the onset of a septic episode were collected retrospectively from patient charts. The following variables were collected: age, NICU stays, antimicrobial therapy exposure (yes/no), additional interventions (surgery, invasive intubation, or use of a ventilator, use of umbilical and central venous catheters or total parenteral nutrition, orogastric feeding tube, urinary catheter, thorax tube), and response to treatment.

Hematological (white blood cell (WBC) count, platelet count), biochemical (C-reactive protein (CRP), blood glucose) and microbiological findings (blood culture, urine culture) of the patients in both groups were recorded and compared.

Statistical Analysis

Summary of measures was reported as the mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. For group comparison, the Mann-Whitney U-test was used for quantitative variables. Categorical data were tested using the Chi-square test. P value ≤ 0.05 was considered statistically significant. All the statistical analyses were performed using SPSS 20 (SPSS Inc., Chicago, IL, USA).

Results

Out of 30,545 babies who were born at the center, 10,133 NICU admissions were recorded during the study period. Of these, 94 neonates diagnosed with sepsis were enrolled. They included 55 (58.5%) females and 39 (41.5%) males. Deliveries were by caesarean section in 54 (57.4 %) cases and vaginal in 40 (42.6%) cases. The mean gestational age (GA) of patients was 30.3 ± 3.8 weeks and mean birth weight (BW) was 1647.1 ± 772.7 g. Seventy-nine (84%) septic neonates had low birth weight (≤ 2500g). Subgrouping identified 48 (51%) with very low birth weight (VLBW) (≤ 1500 g). Mean hospitalization time was 43.6 ± 34.4 days (Table 1). Among the sick newborns, EOS was present in 30 (31.9 %) cases and LOS in 64 (68.1%).

All septic babies had at least a risk factor for neonatal sepsis (Table 2). All patients with EOS had received at least an antibiotic. Total parenteral nutrition (TPN) and mechanical ventilation (MV-CPAP) were the most common risk factors in both EOS and LOS groups. For EOS patients, umbilical venous catheter was found in 23 (76.7%), TPN in 19 (63.3%), MV and CPAP in 23 (76.6%). For LOS babies, MV or CPAP was present in 27 (42.1%), and 18 (28.1%) patients had TPN (Table 2). 19 (29.7%) patients with LOS had received one or more antibiotics before a septic attack.

The median skin temperature was 36.6ºC (interquartile range [IQR]: 0.90). Minimum and maximum skin temperatures were 36.0ºC and 39.4ºC respectively. Besides, 55 (58.5%) cases had normal temperature, 34 (36.2%) had hyperthermia, and 5 (5.3%) had hypothermia (1). Median skin temperatures between EOS and LOS groups were comparable (for EOS, 36.80C; for LOS, 36.70C).

Table 1. A Comparison of Early-Onset and Late-Onset Sepsis

	Total	Early-Onset Sepsis (30 newborns)	Late-Onset Sepsis (64 newborns)
GA (weeks)[a]	30.8±3.8	29.8±3.7	29.8±3.7
BW (grams)[a]	1647±772	1902±770	1527±749
VLBW[b]	48	10	40
Male	39	10	29
Sepsis rate[c]	94 (18,8%)	30 (6%)	64 (12.8%)
Sepsis-related death			
<1000 grams BW	7	2	5
<1500 grams BW	6	-	6
1500–2000 grams BW	2	2	-
>2000 grams BW	4	3	1
22–24 weeks' GA	2	-	2
25–29 weeks' GA	10	2	8
30–36 weeks' GA	5	4	1
>36 weeks' GA	2	1	1
Age at onset of late-onset sepsis (day)[a] Skin temperature(ºC)	43.6±34.4	31.4±12.6	40.3±35.2

a: mean±standard deviation
b: as N(%)
c: as cases per 100 NICU participation

Abnormal leukocyte counts were seen in 36 (38.3%) cases. Abnormalities in the complete blood count such as leukopenia (WBC <5,000/mm3), leukocytosis (WBC > 20,000/mm3), and thrombocytopenia (platelets <150,000/mm3) were seen in 24 (25.5%), 12 (12.8%), and 42 (44.7%) patients, respectively (Table 3). Thrombocytopenia was more common among EOS cases but similar to leukocytosis and leukopenia, there were no significant differences between EOS and LOS groups (p=0.30, p=0.06, p=0.13, respectively).

CRP levels were measured in all 94 cases and were found to be positive (>8mg/L) in 55 (58.5%) cases. CRP positivity was not significantly different in the EOS and LOS groups (p=0.48). Blood glucose levels were not significantly associated with the incidence of sepsis (p=0.19).

Table 4 shows the most common causative organisms of neonatal sepsis (early or late-onset sepsis). Ninety-four microorganisms were identified in blood cultures. These consisted of 35 (37.2%) *Klebsiella pneumonia*, 8 (8.5%) *Staphylococcus haemolyticus*, 6 (6.4%) *Staphylococcus epidermidis*, 6 (6.4%) *Serratia marcescens*, 5 (5.3%) *Enterococcus faecium*, 4 (4.3%) *Pseudomonas aeruginosa*, and 4 (4.3%) *Enterobacter cloacae*. *Candida* was grown in the blood of six patients (all LOS patients). Among all cases of LOS, *Klebsiella pneumonia* were the most common organisms isolated with 19 cases (29.7%), followed by *coagulase-negative staphylococci* (CoNS) 18 (28.1%), *Staphylococcus haemolyticus* 7 (11%), *Staphylococcus epidermidis* 6 (9.4%), *Staphylococcus hominis* 1 (1.6%), other 4 (6.3%), *Serratia marcescens* 6 (6.4%) and *Candida* 6 (6.4%) (Table 4). Similarly, *Klebsiella pneumonia* was the most common organism, with 16 (53.3%) isolated in the cases of EOS.

On average, LOS occurred on the day of life 40.3±35.2. Rates of LOS, death and sepsis-related death were inversely proportional to GA and BW (Table 1). LOS episodes attributed to *Klebsiella pneumonia* were associated with the highest sepsis-related mortality (41.7%), followed by *Staphylococcus haemolyticus* (33.3%), *Enterobacter spp* (8.3%), and *Candida* (8.3%).

Discussion

This study aimed to investigate the incidence of culture-proven EOS and LOS in the state of Konya, a region in Turkey, to identify the primary causative organisms of neonatal sepsis, and to highlight the complex interaction of factors involved in the outcome of neonatal sepsis.

Neonatal sepsis is the leading cause of mortality in the neonatal intensive care units [6]. Its prevalence rate in the present study was 2.7 per 1000 live births (94/30545) of 9.3 per 1000 neonatal admissions (94/10133). Nikkhoo et al. [3] have reported a prevalence rate of 6.4% for sepsis. The prevalence of sepsis in their study was twice that of ours. Similar to what has been reported in developed countries [7], the incidence of EOS was 0.98 per 1000 live births. The incidence of LOS was 2.1 per 1000 live births, which is less than that reported from developing countries [8].

Table 2. Risk factors of neonatal sepsis (early and late-onset sepsis) present in study (n=94)

Risk factors	No. of babies (%)
PROM[a]	14 (46.7)
Meconium-stained liquor[a]	7 (23.3)
Low birth weight (<2500 g)[a,b]	EoS: 23 (76.6), LoS: 55 (85.9)
Preterm (<37 weeks) [a,b]	EoS: 25 (83.3), LoS: 57 (89)
Active resuscitation required in labor room[a]	13 (43.3)
Umbilical venous catheter [a]	23(76.7)
Urinary tract infection in the mother [a]	5 (16.7)
MV or nCPAP[a,b]	EoS: 23 (76.6), LOS: 27 (42.1)
Parenteral nutrition[b]	EoS: 19 (63.3), LOS: 18 (28.1)
Orogastric tube[b]	EoS: 30 (all cases), LOS: 34 (53.1)
Vesical catheter	3 (4.7)
Previous antibiotics	19 29.7)
Chest tube	8 (12.5)
Central catheter	8 (12.5)

a: risk factor of early-onset sepsis
b: risk factor of late-onset sepsis

Tablo 4. Microbiological profile found in positive blood cultures from neonates with early- and late-onset sepsis

Isolated microorganism	Total (%)	EOS number (%)	LOS number (%)
Gram-positive			
Staphylococcus aureus	3 (3.2)	2 (6.7)	1 (1.6)
Enterococcus faecalis	5 (5.3)	3 (10)	2 (3.1)
Coagulase-negative staphylococci	5 (5.3)	1 (3.3)	4 (6.3)
Staphylococcushominis	1 (1.1)	-	1 (1.6)
Staphylococcus haemolytic	8 (8.5)	1 (3.3)	7 (11)
Staphylococcusepidermidis	6 (6.4)	-	6 (9.4)
Gram-negative			
Klebsiella pneumonia	35 (37.2)	16 (53.3)	19 (29.7)
Escherichia coli	2 (2.1)	-	2 (3.1)
Enterobacter zero genes	2 (2.1)	-	2 (3.1)
Enterobacter cloacae	4 (4.3)	1 (3.3)	2 (3.1)
Pseudomonas aeruginosa	4 (4.3)	3 (10)	1 (1.6)
Serratia marcescens	6 (6.4)	-	6 (9.4)
Serratia liquefacient	2 (2.1)	-	2 (3.1)
Acinetobacter junni	1 (1.1)	1 (3.3)	-
Acinetobacter baumannii	3 (3.2)	1 (3.3)	2 (3.1)
Brevundimonas diminuta	1 (1.1)	1 (3.3)	-
Fungi			
Candida sp.	6 (6.4)	-	6 (9.4)

A: CoN S not identified

Tablo 3. Correlation of infection markers with EOS and LOS cases

	CRP		WBC		platelets		glucose			
	normal	positive	leukocytosis	leukopenia	normal	thrombocytopenia	normal	hyperglycemia	hypoglycemia	normal
EOS	15	15	3	10	17	9	21	5	2	23
LOS	24	40	9	14	41	33	31	20	4	40
p		0.48	0.06	0.13		0.30		0.19		

In premature newborns, the risk of sepsis and sepsis-related mortality increase as birth weight decreases [9]. In our study, the mortality rate was significantly high among patients with birth weights less than 1500 g. The rate of death was 13.8% below 1500g but decreases to 6.4% above 1500g. In a study by Turhani et al. [2], low birth weight was found to be significantly associated with mortality rates of neonatal sepsis. Sepsis-related mortality was found to be 36.3% in babies with a birth weight <1000g, and 15% in babies with a birth weight >1000g. According to previous studies conducted in Turkey on neonatal sepsis, mortality rates are higher for EOS patients than LOS patients [10]. Conversely, the present study reported higher death rates among LOS patients than EOS patients (12.8 % for LOS, 7.4% for EOS). A greater proportion of patients with BW <1500g within the LOS group can explain this different finding. In the present study, premature rupture of the fetal membranes (PROM), meconium-stained liquor, low birth weight, prematurity, active resuscitation required in the labor room, urinary tract infection in the mother, MV or NCPAP, TPN, orogastric tube, vesical catheter, previous antibiotics, chest tube, and central catheter were associated with neonatal sepsis. Similar findings have been reported in previous studies [11, 12, 13]. Of note, PROM, active resuscitation required in labor room, TPN and MV were significant risk factors for early sepsis, but not for late sepsis. The most important neonatal factor predisposing to neonatal sepsis is prematurity and LBW [3]. Low birth weight and prematurity were major risk factors for early and late sepsis in our study.

The incidence and microbiology of neonatal sepsis vary from region to region. In developed countries, *Group B Streptococcus* is most significant cause of neonatal sepsis [14]. However, in the present study, gram-negative bacteria were more frequently isolated than gram-positive bacteria. These results were consistent with the findings of many previous studies [15,16]. Similarly, the most commonly isolated agents in EOS from different units in Turkey include gram (-) bacilli [17]. In this study, *Klebsiella pneumonia* is reported as the common isolate in both EOS and LOS, followed by *coagulase-negative staphylococci* in LOS and *Enterococcus faecalis* and *Pseudomonas aeruginosa* in EOS. Most of the studies performed in developing countries have shown *Klebsiella pneumonia* as the most implicated gram-negative bacteria for neonatal sepsis [18, 19].

Body temperature, blood glucose level, and various serologic markers such as CRP, WBC counts, and thrombocyte count are often used to support the diagnosis of sepsis [20]. In a study by Ahmad et al. [5], most cases of culture-proven and probable neonatal sepsis found the normal axillary temperature. Similar findings were seen in this study. CRP is an acute phase reactant which is used very frequently in the diagnosis of neonatal sepsis [20]. In this study, CRP levels were found to be high in EOS and LOS. But there was no statistically significant difference in CRP elevation between these two groups. Thrombocytopenia was observed in 55.3% of the patients. This finding supported the results of Turhan et al. [2]. In our study, the thrombocyte count was found to be lower in the babies who were EOS compared to the LOS. But there was no statistically significant difference in thrombocytopenia between these two groups. Turhan et al. [2] found the neutrophil count to be lower in the babies who were lost because of sepsis compared to the mortality from non-sepsis. In our study, there was no statistically significant difference in white blood cell count between these two groups.

There are many metabolic changes during severe sepsis and septic shock, and among the metabolic changes, blood glucose level is the most important [21]. Studies by Ahmad et al. [22] found that blood sugar levels below 40 mg / dL and above 200 mg / dL had higher mortality rates. However, in our study, there was no relationship between blood glucose level and sepsis.

In conclusion, *Klebsiella pneumonia* was the most commonly found organism in this study and was responsible for the mortality associated with sepsis in this study. This study has demonstrated an increased incidence of sepsis in VLBW and premature babies. Prevalence of neonatal sepsis, its pathogens, and risk factors are different across the world. In each NICU, strategies aimed at prevention of neonatal infection such as reinforcement of infection control policies, selecting correct antibiotics, and providing information regarding the frequently isolated organisms and their drug resistance patterns should be implemented.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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